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Laboratory note

Synthesis and cytotoxic evaluation of α-methylene-γ-butyrolactone bearing naphthalene and naphtho[2,1-*b*]furan derivatives

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Abstract

Naphthalene α-methylene-γ-butyrolactones exhibits a unique cytotoxicity profile. They are highly cytostatic for leukaemia cancer cells but are not cytocidal. For almost all the solid tumours tested, they are both cytostatic and cytocidal. Substitution of a bromo atom on either naphthalene or both naphthalene and γ-phenyl moiety of the lactone enhanced potency while retaining the same cytotoxicity profile. The tricyclic naphtho[2,1-*b*]furan derivatives, prepared from 2-hydroxy-1-naphthaldehyde in an efficient pathway, also possess the same cytotoxicity profile.

Keywords: cytotoxicity; naphtho[2,1-*b*]furan; naphthalene; α-methylene-γ-butyrolactone

1. Introduction

The bicyclic naphthalene skeleton constitutes a large number of clinical drugs, such as propranolol (**I**) [1], naphazoline (**II**; a cardiovascular agent) [2], naproxen (**III**) [3], nabumetone (**IV**; an anti-inflammatory agent) [4] and methallenestril (**V**; a non-steroid oestrogen) (Fig. 1). The α-methylene-γ-butyrolactone moiety is a characteristic component of a large number of natural products which produce wide-ranging biological activities, including antitumour, bactericidal, fungicidal, antibiotic, and anthelminthic properties [5–7]. Recently, we have reported certain α-methylene-γ-butyrolactone bearing uracil (**VI**) [8,9], naphthalene (**VII**), quinoline (**VIII**), and quinolin-2(1*H*)-one (**IX**) as potential antitumour agents [10,11] (Fig. 2). Although quinolin-2(1*H*)-one α-methylene-γ-butyrolactones were the most cytotoxic, naphthalene derivatives, **1** and **2** (Fig. 3), also exhibited a distinct cytotoxicity profile. They are cytostatic for leukaemia cancer cells but are both cytostatic and cytocidal for most of the solid tumours tested. To optimise the potency and retain their cytotoxicity profile, structural modifications were carried out on naphthalene α-methylene-γ-butyrolactone by substitution of a bromo atom on the γ-phenyl moiety of the lactone ring and/or naphthalene skeleton. Benzofuran nucleus is found in various naturally occurring compounds, and a number of their natural and synthetic derivatives are known to exhibit interesting biological properties [12]. Thus, the tricyclic naphtho[2,1-*b*]furan derivatives, **9a** and **9b**, which containing the benzofuran moiety were also synthesised from 2-hydroxy-1-naphthaldehyde (**6**) in an efficient pathway. Preparation and cytotoxic evaluation of the title compounds are described.

2. Chemistry

Synthesis of 2-[(1-bromonaphthalen-2-yloxy)methyl]-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenylfuran (**5a**) and its derivatives, **5b** and **5c**, is illustrated in Fig. 4. 1-Bromo-2-naphthol (**3**) was treated with K_2CO_3 and 2-bromoacetophenone to give 2-(1-bromonaphthalen-2-yloxy)-1-phenylethan-1-one (**4a**) in 72% yield. Accordingly, **4b** and **4c** were prepared in a yield of 73 and 79%, respectively, from **3** and 4-substituted 2-bromoacetophenones. *Reformatsky*-type condensation of **4a–c** to afford the target **5a–c** proceeded smoothly in a

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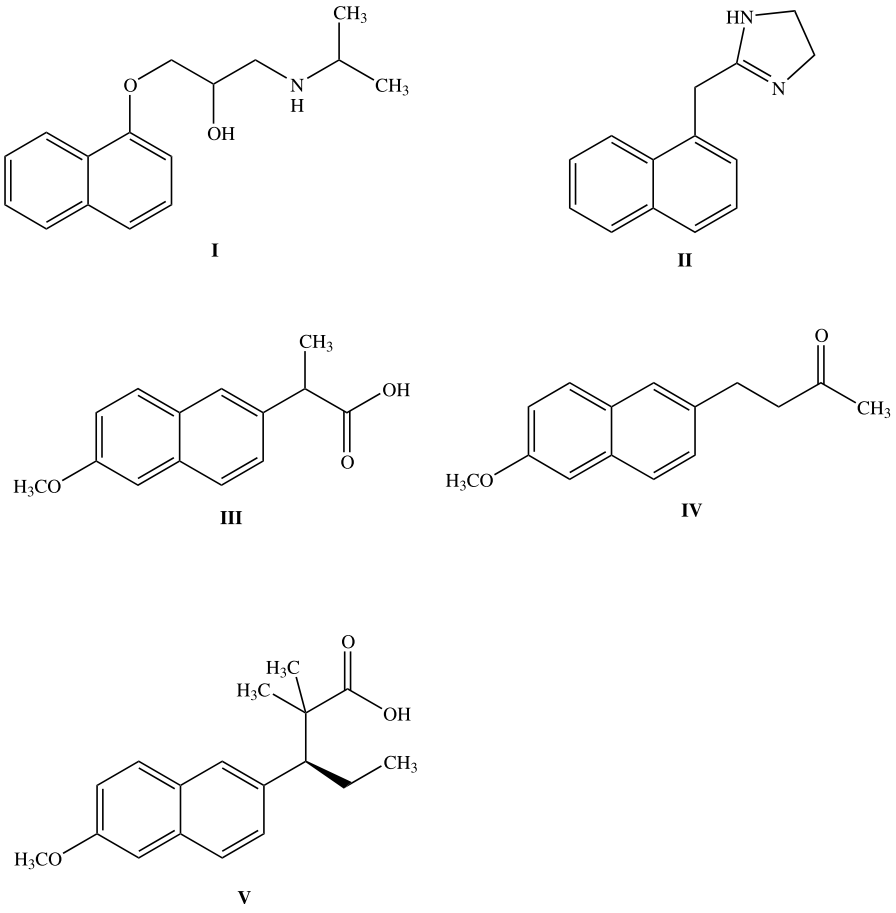
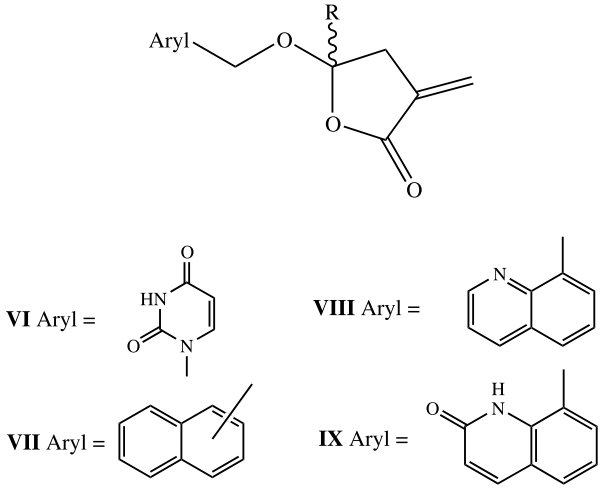


Fig. 1. The bicyclic naphthalene skeleton containing propanolol (**I**), naphazoline (**II**), naproxen (**III**), nabumetone (**IV**), and methallenestril (**V**).

fairly good yield (83, 72 and 81%, respectively). Synthesis of compounds **1** and **2** was previously reported [11].

Preparation of naphtho[2,1-*b*]furan α-methylene-γ-butyrolactones **9a** and **9b** is depicted in (Fig. 5). 2-Hydroxy-1-naphthaldehyde (**6**) was alkylated with chloroacetone under basic condition to give 1-methyl-2-(1-naphthaldehyde-2-yloxy)ethan-1-one (**7**) as an intermediate which immediately cyclised through an intramolecular *Aldol*-type condensation to afford 1-(naphtho[2,1-*b*]furan-2-yl)ethan-1-one (**8a**) in a 76% yield [13–16]. Compound **8a** was previously synthesised from the reaction of 2-naphthol and 3,4-dibromobutan-2-one followed by oxidation with DDQ in an overall yield of 54% [17]. Naphtho[2,1-*b*]furan-2-yl phenyl methanone (**8b**), formerly synthesised by the condensation of 2-methoxy-1-naphthaldehyde and acetophenone [18] followed by copper (II)-mediated photocyclisation [19] in a 51% overall yield. This compound can be easily obtained in 87% from **6** and 2-bromoacetophenone in one step. *Reformatsky*-type condensation of **8a** and **8b** afforded the desired **9a** and **9b**, respectively.



R = CH_3, C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-MeO-C_6H_4, and 4-ph-C_6H_4

Fig. 2. α-Methylene-γ-butyrolactone bearing uracil (**VI**), naphthalene (**VII**), quinoline (**VIII**), and quinolin-2(1*H*)-one (**IX**) derivatives.

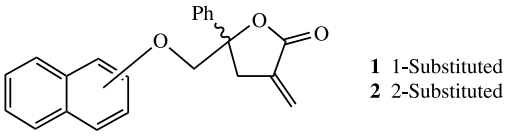


Fig. 3. The structure of the α-methylene-γ-butyrolactone bearing naphthalene derivatives.

3. Results and discussion

All compounds were evaluated in vitro against 60 human tumour cell lines derived from nine cancer cell types (leukaemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer). For each compound, dose–response curves for each cell line were measured with five different drug concentrations, the concentration causing 50% cell growth inhibition (GI_{50}; equating to cytostatic activity) and the concentration causing 50% cell death (LC_{50}; equating to cytocidal activity) compared with the control were calculated [20] and summarised in Table 1. All these compounds demonstrated potent growth inhibitory activities against leukaemia cancer cells ($\log GI_{50} < -5.0$). α-Methylene-γ-butyrolactone bearing naphtho[2,1-*b*]furans (**9a** and **9b**) and naphthalenes (**1** and **2**) were comparable in the inhibitory activity on human leukaemia cancer cells. 1-Bromonaphthalene derivatives **5a**–**c** exhibited a more potent growth inhibitory activity (cytostatic) on leukaemia than the parent naphthalene counterparts **1** and **2**. The average $\log GI_{50}$ decreased in an order **5c** (−6.45) > **5a** (−6.37) > **5b** (−5.92) > **1** (−5.81) > **9a** (−5.70) > **2** (−5.64), **9b** (−5.61). However, none of them were able to effectively cause cell death of leukaemia ($\log LC_{50} > -4.0$). For solid tumours, the difference between GI_{50} and LC_{50} was relatively small, indicating these α-methylene-γ-butyrolactones were able to not only inhibit cell growth but also kill the cells. The average $\log GI_{50}$ and the average $\log LC_{50}$ decreased in an order **5c** (−5.91; −5.33) >

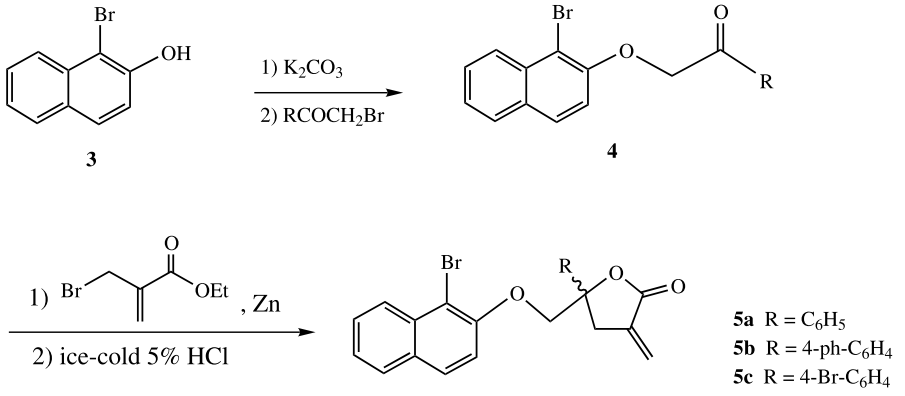


Fig. 4. Sythesis of α-methylene-γ-butyrolactone bearing 1-bromonaphthalene derivatives **5a**–**c**.

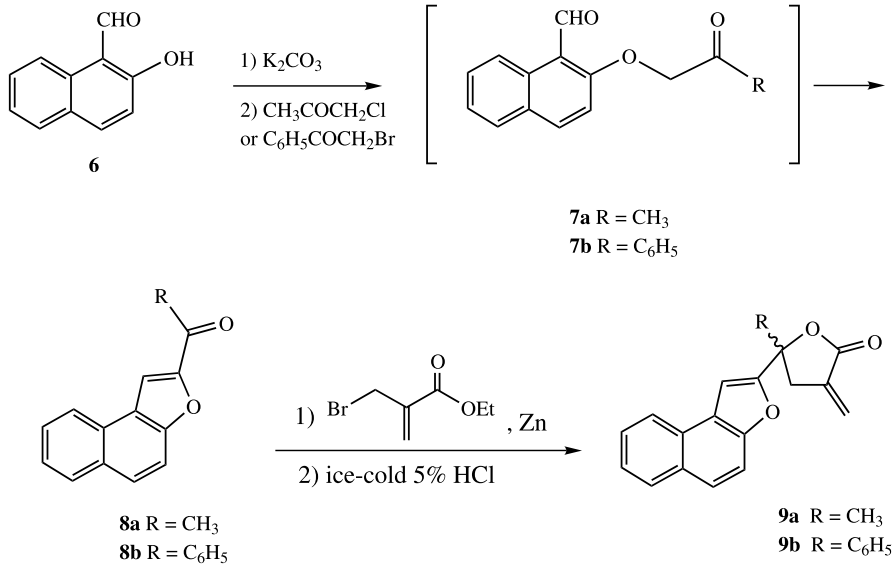


Fig. 5. Synthesis of α-methylene-γ-butyrolactone bearing naphthol[2,1-*b*]furans **9a**–**b**.

Table 1
Inhibition of in vitro human cancer cells by α-methylene-γ-butyrolactones [log GI_{50} (log LC_{50})(M)] [a]

Cell line	1	2	5a	5b	5c	9a	9b
Leukaemia							
CCRF-CEM	−5.81 (> −4.0)	−5.77 (> −4.0)	−6.46 (> −4.0)	−6.33 (> −4.0)	−6.62 (> −4.0)	−5.81 (> −4.0)	−5.92 (> −4.0)
HL-60(TB)	−5.76 (> −4.0)	−5.86 (> −4.0)	−6.67 (> −4.0)	−6.51 (> −4.0)	−6.76 (> −4.0)	Nd [b] (> −4.0)	−5.64 (> −4.0)
K-562	−5.43 (> −4.0)	−5.57 (> −4.0)	−6.27 (> −4.0)	−5.78 (> −4.0)	−6.23 (> −4.0)	−5.58 (> −4.0)	−5.56 (> −4.0)
MOLT-4	−5.55 (> −4.0)	−5.50 (> −4.0)	−6.53 (> −4.0)	−5.66 (> −4.0)	−6.65 (> −4.0)	nd	−5.50 (> −4.0)
RPMI-8226	−5.64 (> −4.0)	−5.65 (> −4.0)	−6.25 (> −4.0)	−5.71 (> −4.0)	−6.37 (> −4.0)	nd	−5.67 (> −4.0)
SR	−6.64 (> −4.0)	−5.48 (> −4.0)	−6.04 (> −4.0)	−5.51 (> −4.0)	−6.09 (> −4.0)	nd	−5.38 (> −4.0)
L-Average [c]	−5.81 (> −4.0)	−5.64 (> −4.0)	−6.37 (> −4.0)	−5.92 (> −4.0)	−6.45 (> −4.0)	−5.70 (> −4.0)	−5.61 (> −4.0)
Solid cancers							
HOP-92	−5.78 (−5.06)	−5.84 (−5.04)	−5.98 (−5.10)	−6.38 (nd)	−5.97 (nd)	−5.86 (−5.22)	−5.63 (−4.71)
KM12	−5.44 (−4.44)	−5.66 (−4.65)	−5.67 (−4.95)	−5.74 (−5.06)	−5.80 (−5.18)	−5.69 (−4.45)	−5.00 (−4.16)
U-251	−5.45 (−4.43)	−5.55 (−4.57)	−5.75 (−5.22)	−5.74 (−5.21)	−5.84 (−5.20)	−5.92 (−5.26)	−5.74 (−5.21)
UACC-62	−5.52 (−4.45)	−5.30 (−4.38)	−5.77 (−5.15)	−5.79 (−5.16)	−5.86 (−5.26)	nd	−5.39 (−4.41)
IGROV1	−5.79 (−5.11)	−5.81 (−4.84)	−5.96 (−5.25)	−5.80 (−5.11)	−5.94 (−5.26)	−5.78 (> −4.0)	−5.53 (−4.14)
786-0	−5.84 (−5.26)	−5.83 (−5.25)	−5.85 (−5.27)	−5.84 (−5.18)	−6.02 (−5.17)	−5.92 (−5.26)	−5.76 (−5.08)
PC-3	−5.39 (−4.38)	−5.19 (−4.36)	−5.64 (−4.49)	−5.69 (−4.74)	−5.90 (−5.30)	−5.79 (−5.18)	−5.00 (−4.33)
BT-549	−5.99 (−5.28)	−5.72 (−4.89)	−6.14 (−5.20)	−5.80 (−5.22)	−5.97 (nd)	−5.75 (−4.62)	−5.66 (−4.70)
S-Average [d]	−5.65 (−4.80)	−5.61 (−4.75)	−5.85 (−5.08)	−5.85 (−5.10)	−5.91 (−5.33)	−5.82 (−4.86)	−5.46 (−4.59)
Mean [e]	−5.50 (−4.59)	−5.48 (−4.52)	−5.76 (−4.63)	−5.71 (−4.53)	−5.92 (−4.85)	−5.74 (−4.64)	−5.35 (−4.32)

[a] Data obtained from NCIs in vitro disease-oriented tumour cell screen [20]. GI_{50}: drug molar concentration causing 50% cell growth inhibition; LC_{50}: drug molar concentration causing 50% cell death.
[b] Not determined.
[c] Average log GI_{50} and log LC_{50} values for six leukaemia cancer cells.
[d] Average log GI_{50} and log LC_{50} values for eight solid cancer cells.
[e] Mean values over all cell lines tested. Theses cell lines are: leukaemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, PRMI-8226, and SR); non-small cell lung cancer (A549/ATCC, EKVX, HOP-62, HOP-92, NCI-H226, NCI-H23, NCI-H322M, and NCI-H522); colon cancer (COLC 205, HCC-2998, HCT-116, HCT-15, HT29, KM12, and SW-620); CNS cancer (SF-268, SF-295, SF-539, SNB-19, SNB-75, and U251); melanoma (LOX IMVI, MALME-3M, M14, SK-MEL-2, SK-MEL-28, SK-MEL-5, and UACC-257); ovarian cancer (IGROV1, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, and SK-OV-3); renal cancer (786-0, A498, ACHN, CAKI-1, RXF 393, SN12C, TK-10, and UO-31); prostate cancer (PC-3 and DU-145); and breast cancer (MCF7, MCF7/ADR-RES, MDA-MB-231/ ATCC, HS 578T, MDA-MB-435, MDA-N and T-47D).

5a (−5.85; −5.08), **5b** (−5.85; −5.10) > **9a** (−5.82; −4.86) > **1** (−5.65; −4.80) > **2** (−5.61; −4.75) > **9b** (−5.46; −4.59). Among them, 2-[(1-bromonaphthalen-2-yloxy)methyl]-2-(4-bromophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxofuran (**5c**) is the most cytotoxic with a mean log GI_{50} value of −5.92.

4. Conclusion

α-Methylene-γ-butyrolactone bearing naphthalene, 1-bromonaphthalene, and naphtho[2,1-*b*]furan exhibited a unique cytotoxicity profile. They are highly cytostatic for leukaemia cancer cells but are not cytocidal. However, they are both cytostatic and cytocidal for almost all the solid tumours tested. Among them, 2-[(1-bromonaphthalen-2-yloxy)methyl]-2-(4-bromophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxofuran (**5c**) is the most cytotoxic with an average log GI_{50} value of −6.45 against the growth of six leukaemia cancer cells, an average log GI_{50} value of −5.91 against the growth of eight solid cancer cells, and a mean log GI_{50} value of −5.92 against all 60 cancer cell tested.

5. Experimental protocols

5.1. Chemistry

Melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. The ultraviolet (UV) absorption spectra were obtained on a Beckman UV–Visible spectrophotometer. Nuclear magnetic resonance (NMR) (^1H and ^{13}C) spectra were recorded on a Varian Gemini-200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Thin-layer chromatography (TLC) was run on precoated (0.2 mm) Silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave UV light (254 nm) was used to detect the UV-absorbing spots. Elemental analyses were carried out in the Instrument Center of National Science Council at National Cheng-Kung

University using Heraeus CHN-O-Rapid elemental analyser, and all values are within ±0.4% of the theoretical compositions.

*5.1.1. 2-(1-Bromonaphthalen-2-yloxy)-1-phenylethan-1-one (**4a**)*

1-Bromo-2-naphthol (**3**, 2.23 g, 10 mmol), K_2CO_3 (1.52 g, 11 mmol) and dry DMF (20 mL) were stirred at r.t. for 30 min. To this solution was added 2-bromoacetophenone (2.19 g, 11 mmol) in dry DMF (10 mL) in one portion. The resulting mixture was stirred at r.t. for 48 h (TLC monitoring), then poured into ice-water (100 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with H_2O, dried (Na_2SO_4), and evaporated. The solid residue was crystallised from CH_2Cl_2 and Et_2O (1:10) to afford **4a** (2.46 g, 72%). m.p.: 114–115 °C; ^{1}H-NMR ($CDCl_3$-*d*): δ 5.48 (s, 2H, OCH_2), 7.16–8.27 (m, 11H, Ar); ^{13}C-NMR ($CDCl_3$-*d*): δ 72.74 (OCH_2), 110.16, 115.34, 124.84, 126.38, 127.80, 128.03, 128.26, 128.83, 128.95, 130.37, 133.15, 133.96, 134.36, 152.61, 194.19 (C=O). Anal. Found: C, 63.14; H, 3.80. Calc. for $C_{18}H_{13}BrO_2$: C, 63.36; H, 3.84%.

*5.1.2. 2-(1-Bromonaphthalen-2-yloxy)-1-(1,1′-biphenyl-4-yl)ethan-1-one (**4b**)*

From **3** and 2-bromo-4′-phenylacetophenone as described for **4a**: 73% yield. m.p.: 144–145 °C; ^{1}H-NMR ($CDCl_3$-*d*): δ 5.51 (s, 2H, OCH_2), 7.19–8.28 (m, 15H, Ar); ^{13}C-NMR ($CDCl_3$-*d*): δ 72.85 (OCH_2), 110.15, 115.34, 124.83, 126.39, 127.26, 127.41, 127.81, 128.04, 128.41, 128.92, 128.97, 130.39, 133.04, 133.17, 139.64, 146.62, 152.63, 193.86 (C=O). Anal. Found: C, 68.85; H, 4.31. Calc. for $C_{24}H_{17}BrO_2$: C, 69.08; H, 4.11%.

*5.1.3. 2-(1-Bromonaphthalen-2-yloxy)-1-(4-bromophenyl)ethan-1-one (**4c**)*

From **3** and 2-bromo-4′-bromoacetophenone as described for **4a**: 79% yield. m.p.: 129–130 °C; ^{1}H-NMR ($CDCl_3$-*d*): δ 5.39 (s, 2H, OCH_2), 7.16–8.27 (m, 10H, Ar); ^{13}C-NMR ($CDCl_3$-*d*): δ 72.82 (OCH_2), 110.16, 115.14, 124.95, 126.37, 127.90, 128.04, 129.04, 129.28, 129.93, 130.40, 132.14, 133.05, 133.12, 152.37, 193.60 (C=O). Anal. Found: C, 51.70; H, 2.95. Calc. for $C_{18}H_{12}Br_2O_2$: C, 51.46; H, 2.88%.

*5.1.4. 2-[(1-Bromonaphthalen-2-yloxy)methyl]-2,3,4,5-tetrahydro-4-methylene-5-oxo-2-phenylfuran (**5a**)*

To a solution of 2-(1-bromonaphthalen-2-yloxy)-1-phenylethan-1-one (**4a**, 0.68 g, 2 mmol) in dry THF (60 mL) were added activated zinc powder (0.17 g, 2.6 mmol), hydroquinone (4 mg), and ethyl 2-(bromomethyl)acrylate (0.52 g, 2.6 mmol). The mixture was refluxed under nitrogen atmosphere for 6 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl solution (200 mL), and extracted with CH_2Cl_2 (3 × 75 mL). The CH_2Cl_2 extracts were combined, washed with H_2O, dried (Na_2SO_4), and evaporated to give a residual solid which was crystallised from CH_2Cl_2 and Et_2O (1:5) to afford **5a** (0.68 g, 83%). m.p.: 160–161 °C; ^{1}H-NMR ($CDCl_3$-*d*): δ 3.27 (dt, 1H, *J* = 17.0, 2.6 Hz, C-3′-H), 3.91 (dt, 1H, *J* = 17.0, 2.6 Hz, C-3′-H), 4.22 and 4.37 (AB type, 2H, *J* = 10.2 Hz, OCH_2), 5.74 (t, 1H, *J* = 2.6 Hz, CH_2=C-4′), 6.34 (t, 1H, *J* = 2.6 Hz, CH_2=C-4′), 7.12–8.23 (m, 11H, Ar). ^{13}C-NMR ($CDCl_3$-*d*): δ 37.30 (C-3′), 75.91 (OCH_2), 84.21 (C-2′), 110.14, 115.21, 122.34, 124.84 (CH_2=C-4′), 125.22, 126.35, 127.84, 128.05, 128.55, 129.02, 130.33, 133.09, 140.39, 152.45, 169.30 (C=O). Anal. Found: C, 64.23; H, 4.24. Calc. for $C_{22}H_{17}BrO_3$: C, 64.57; H, 4.19%.

*5.1.5. 2-[(1-Bromonaphthalen-2-yloxy)methyl]-2,3,4,5-tetrahydro-4-methylene-2-(1,1′-biphenyl-4-yl)-5-oxofuran (**5b**)*

From **4b**, as described for **5a**: Yield 72%. m.p.: 108–109 °C. ^{1}H-NMR ($CDCl_3$-*d*): δ 3.32 (dt, 1H, *J* = 16.9, 2.6 Hz, C-3′-H), 3.95 (dt, 1H, *J* = 16.9, 2.6 Hz, C-3′-H), 4.22 and 4.37 (AB type, 2H, *J* = 10.2 Hz, OCH_2), 5.76 (t, 1H, *J* = 2.6 Hz, CH_2=C-4′), 6.36 (t, 1H, *J* = 2.6 Hz, CH_2=C-4′), 7.15–8.24 (m, 15H, Ar). ^{13}C-NMR ($CDCl_3$-*d*): δ 37.31 (C-3′), 75.85 (OCH_2), 84.14 (C-2′), 110.15, 115.21, 122.46, 124.85 (CH_2=C-4′), 125.71, 126.35, 127.11, 127.44, 127.68, 127.84, 128.05, 128.87, 129.03, 130.34, 133.09, 134.56 (C-4′), 139.30, 140.22, 141.54, 152.45, 169.26 (C=O). Anal. Found: C, 69.30; H, 4.47. Calc. for $C_{28}H_{21}BrO_3$: C, 69.29; H, 4.36%.

*5.1.6. 2-[(1-Bromonaphthalen-2-yloxy)methyl]-2-(4-bromophenyl)-2,3,4,5-tetrahydro-4-methylene-5-oxofuran (**5c**)*

From **4c**, as described for **5a**: Yield 81%. m.p.: 138–139 °C. ^{1}H-NMR ($CDCl_3$-*d*): δ 3.22 (dt, 1H, *J* = 16.9, 2.6 Hz, C-3′-H), 3.89 (dt, 1H, *J* = 16.9, 2.6 Hz, C-3′-H), 4.22 and 4.37 (AB type, 2H, *J* = 10.2 Hz, OCH_2), 5.75 (t, 1H, *J* = 2.6 Hz, CH_2=C-4′), 6.35 (t, 1H, *J* = 2.6 Hz, CH_2=C-4′), 7.11–8.23 (m, 10H, Ar). ^{13}C-NMR ($CDCl_3$-*d*): δ 37.26 (C-3′), 75.54 (OCH_2), 83.67 (C-2′), 110.14, 115.10, 122.75, 122.85, 124.93 (CH_2=C-4′), 126.33, 127.05, 127.90, 128.06, 129.09, 130.37, 131.90, 133.05, 134.10 (C-4′), 139.45, 152.27, 168.93 (C=O). Anal. Found: C, 53.95; H, 3.38. Calc. for $C_{22}H_{16}Br_2O_3$: C, 54.13; H, 3.30%.

*5.1.7. 1-(Naphtho[2,1-b]furan-2-yl)ethan-1-one (**8a**)*

2-Hydroxy-1-naphthaldehyde (**6**, 1.72 g, 10 mmol), K_2CO_3 (3.04 g, 22 mmol) and dry DMF (20 mL) were stirred at r.t. for 30 min. To this solution was added dropwise chloroacetone (1.38 g, 15 mmol) in dry DMF (10 mL). The resulting mixture was stirred at r.t. for 48 h. (TLC monitoring), then poured into ice-water (100

mL), and extracted with CH_2Cl_2 (3×20 mL). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The solid residue was crystallised from EtOAc to give 1.60 g of **8a**, m.p. 132–133 °C [17] in 76% yield.

*5.1.8. Naphtho[2,1-b]furan-2-yl phenyl methanone (**8b**)*

From **6** and 2-bromoacetophenone as described for **8a** [18,19]: 87% yield.

*5.1.9. 2,3,4,5-Tetrahydro-2-methyl-4-methylene-2-(naphtho[2,1-b]furan-2-yl)-5-oxofuran (**9a**)*

To a solution of **8a** (0.42 g, 2 mmol) in dry THF (30 mL) were added activated zinc powder (0.17 g, 2.6 mmol), hydroquinone (4 mg), and ethyl 2-(bromomethyl)acrylate (0.52 g, 2.6 mmol). The mixture was refluxed under nitrogen atmosphere for 10 h (TLC monitoring). After cooling, it was poured into an ice-cold 5% HCl solution (200 mL), and extracted with CH_2Cl_2 (3×75 mL). The CH_2Cl_2 extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to give a residual solid which was crystallised from EtOAc to give **9a** (0.44 g, 80%). m.p. 123–124 °C. ^{1}H-NMR ($CDCl_3$-*d*): δ 1.57 (s, 3H, CH_3), 3.06 (dt, 1H, $J = 16.7$, 2.6 Hz, C-3′-H), 3.52 (dt, 1H, $J = 16.7$, 2.6 Hz, C-3′-H), 5.73 (t, 1H, $J = 2.6$ Hz, CH_2 = C-4′), 6.35 (t, 1H, $J = 2.6$ Hz, CH_2 = C-4′), 7.20 (s, 1H, CH), 7.26–8.11 (m, 6H, Ar). ^{13}C-NMR ($CDCl_3$-*d*): δ 26.09 (CH_3), 39.66 (C-3′), 79.54 (C-2′), 102.49 (CH), 112.41, 123.01, 123.14, 123.39, 124.87 (CH_2=C-4′), 126.03, 126.71, 127.85, 128.94, 130.51, 134.73 (C-4′), 152.85, 156.68, 169.58 (C=O). Anal. Found: C, 77.55; H, 5.41. Calc. for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07%.

The same procedure was used to convert **8b** to **9b**.

*5.1.10. 2,3,4,5-Tetrahydro-4-methylene-2-(naphtho-[2,1-b]furan-2-yl)-5-oxo-2-phenylfuran (**9b**)*

Yield: 79%. m.p. 179–180 °C. ^{1}H-NMR ($CDCl_3$-*d*): δ 3.50 (dt, 1H, $J = 16.8$, 2.6 Hz, C-3′-H), 4.01 (dt, 1H, $J = 16.8$, 2.6 Hz, C-3′-H), 5.76 (t, 1H, $J = 2.6$ Hz, CH_2 = C-4′), 6.37 (t, 1H, $J = 2.6$ Hz, CH_2 = C-4′), 6.96 (s, 1H, CH), 7.26–7.99 (m, 12H, Ar). ^{13}C-NMR ($CDCl_3$-*d*): δ 40.48 (C-3′), 82.54 (C-2′), 105.14 (CH), 112.44, 112.50, 122.92, 123.17, 123.41, 124.90 (CH_2=C-4′), 125.74, 126.27, 126.71, 127.84, 128.82, 128.91, 130.49, 134.10 (C-4′), 140.94, 153.20, 156.28, 169.29 (C=O). Anal. Found: C, 81.44; H, 5.13. Calc. for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74%.

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